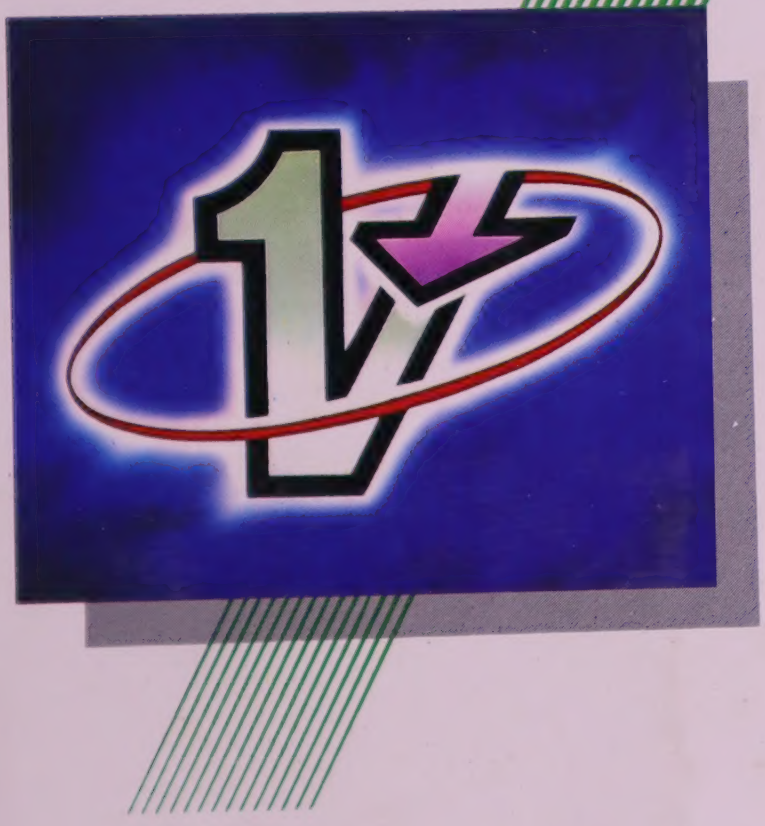
Vibazine* DT

doxycycline monohydrate 100 mg tablets



CLINICAL MONOGRAPH

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INTRODUCTION

VIBAZINE DT (doxycycline monohydrate) is a broad spectrum antibiotic of the tetracycline group. The first tetracycline was discovered in 1948, and since then the tetracyclines have been the subject of extensive research over decades, during which time there were many pharmacologically distinct analogues successfully developed. All tetracycline analogues share the same major advantage: broad-spectrum antibiotic activity -- the ability to inhibit the growth of many Gram-positive and Gram-negative bacterial species, as well as that of certain other micro-organisms. Each of the antibiotics in this class may also produce a pattern of similar adverse reactions.

Generally, while these effects do not differ in kind, they can differ greatly in degree and incidence. The causative principle of this phenomenon is thought to be the same pharmacodynamic principle which governs the drug's absorption, tissue distribution, excretion pattern, persistence in the body, amount and frequency of dosage.

However, doxycycline represents an advanced analogue of all the tetracyclines, embodying many features that make it the logical choice when broad-spectrum therapy is being considered.

Doxycycline has several outstanding characteristics which the older tetracyclines do not share.

1. With doxycycline, absorption is virtually complete, with most of the drug being absorbed during the first hour after oral administration. The maintenance dosage of doxycycline after the first day is only one-tenth the quantity of tetracycline ordinarily given for bacterial infections of like severity.

2. Doxycycline can be administered with food or milk without markedly impairing its absorption. Administration of doxycycline with meals reduces any tendency to nausea.

3. As a result of its optimal lipophilicity, doxycycline efficiently penetrates the tissues and reaches many body fluids in biologically active concentrations. Most significantly, doxycycline has been found to penetrate inflamed tissues, so ensuring that the antibiotic reaches the site of infection.

4. The rapid and virtually complete absorption of doxycycline causes minimal disturbance of intestinal flora, which markedly reduces the incidence of lower gastro-intestinal (GI) side effects.

5. The rate of excretion is slow, so that doxycycline may be given once daily at comparatively low dosage.

6. Although under normal conditions the concentration of doxycycline in the urine is generally high, there is no need for dose reduction in patients with moderately or severely impaired renal function. The GI tract provides an alternative route of excretion. Further, since the drug is secreted in a biologically inactive form into the lumen of the GI tract, doxycycline does not accumulate in the serum. Doxycycline does not share the anti-anabolic effects of other tetracyclines; blood urea nitrogen is not significantly increased during doxycycline therapy even in cases of renal insufficiency.

7. A single daily maintenance dose of 100 mg doxycycline may be given for treatment of less severe infections following the first-day loading dose of 200 mg. For more severe infections a maintenance dose of 200 mg daily is recommended. The advantages of less frequent dosing include increased convenience for the patient, along with the potential for better patient compliance.

DOXYCYCLINE - A SUMMARY

PHARMACOKINETICS

Absorption after oral administration is virtually complete and unaffected by the presence or absence of food in the stomach. Most of the drug is absorbed during the first hour.

Doxycycline has an optimum lipid solubility (lipophilicity) which is responsible for the rapid and complete absorption from the gut, and allows the drug to penetrate readily into tissues and areas of inflammation.

Doxycycline is highly bound to plasma proteins and has a serum half-life of about 22 hours; i.e. excretion is slow. This half-life is longer than that of other tetracyclines.

Effective therapeutic levels in the serum can thus be obtained with once-a-day oral doses. The maintenance dose is low compared with that of other tetracyclines; this implies a potentially lower incidence of side-effects.

Tissue levels in inflamed lung and bronchial wall exceed the MICs of the common infecting organisms. Levels within the therapeutic range are found in many other tissues and body fluids.

Biliary excretion accounts for only a small percentage of doxycycline recoverable from the faeces. The major part of the doxycycline excreted in the faeces has been secreted by the blood stream into the lumen of the small intestine. Here it is bound to the contents in a biologically inactive form; thus it has little or no effect on the normal intestinal flora.

Doxycycline is excreted only in part by the kidney. In the presence of normal renal function or renal insufficiency, it does

not provoke a rise in BUN. Excretion of doxycycline in cases of impaired renal function is via the intestinal wall route.

MICROBIOLOGY

Doxycycline is a true broad spectrum antibiotic with a wide range of activity against both Gram-positive and Gram-negative bacteria, as well as a variety of other micro-organisms (including rickettsiae, chlamydiae, and mycoplasmas).

Doxycycline is bacteriostatic and acts mainly by interfering with protein synthesis.

Doxycycline has the outstanding advantage over other tetracyclines of causing minimal disturbance to the normal intestinal fora. This is due to its rapid and complete absorption and its excretion in a highly bound, biologically inactive form.

CLINICAL USES

Respiratory infections of all types, whether upper or lower in location, are the most important indications for treatment with doxycycline. The drug is often regarded as the antibiotic of first choice in these cases. The main organisms commonly responsible for respiratory infections are sensitive to doxycycline.

The properties of doxycycline make it particularly suitable for the long-term prophylactic management of patients with chronic bronchitis.

Doxycycline is useful for both acute and chronic infections of the urinary tract. In patients with renal failure there is an absence of harmful effects on renal function, the drug does not accumulate in the body, and the dosage does not have to be adjusted or the blood levels monitored.

Doxycycline is effective in the treatment of gonorrhoea and non-gonococcal urethritis (which may be caused by T-mycoplasma). The short dosage schedule does not mask the presence of co-existing syphilis. In appropriate dosage the antibiotic is an efficient treatment for syphilis.

Rickettsial infections are particularly amenable to treatment with doxycycline. In epidemic louse-borne typhus fever, single-dose mass therapy may prove to have a major impact on public health control.

Doxycycline is also of value in the treatment of infections of the ear, nose, and throat, of the skin, of the gastrointestinal and biliary tracts, and in gynecologic and surgical (both pre-operative and post-operative) infections.

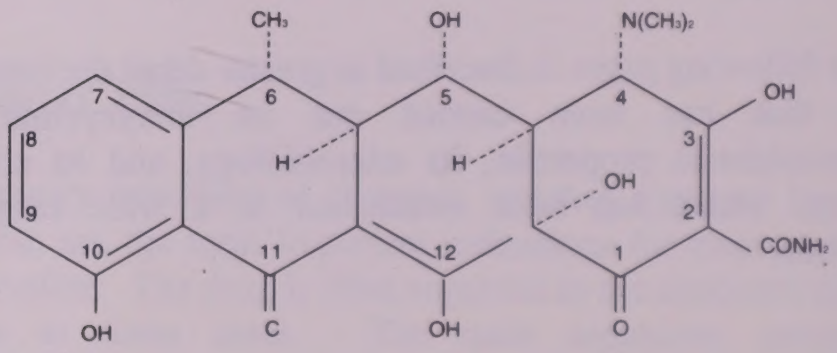
In ophthalmology, doxycycline is a promising antibiotic for the mass therapy of trachoma.

On the following pages is described in greater detail the intensive work that has been carried out on doxycycline, its pharmacokinetic properties, its microbiology, and its clinical efficacy, which has been established in a wide range of infections.

CHEMISTRY

DESCRIPTION

VIBAZINE DT (doxycycline monohydrate) is a broad-spectrum antibiotic synthetically derived from methacycline. The chemical designation of this light-yellow crystalline powder is α6-deoxy-5-oxytetracycline. Its monohydrate salt has a molecular weight of 462.46 and a molecular formula $C_{22}H_{24}N_2O_8.H_2O$. The structural formula of doxycycline is shown below:



Doxycycline is synthesized from oxytetracycline by one of several sequential operations. Two salts of doxycycline are used in oral dosage forms -- doxycycline hydrochloride hemiethanolate hemihydrate (abbreviated as doxycycline hyclate) and doxycycline monohydrate, the water-insoluble amphoteric base prepared from the hyclate. Dosage quantities are expressed as the equivalent amount of anhydrous doxycycline base. Upon absorption these salts are indistinguishable from one another, and are hereafter referred to as "doxycycline".

THE MONOHYDRATE ADVANTAGE

A 1% aqueous suspension of doxycycline monohydrate has a pH of 5.0 to 6.5; the hyclate or hydrochloride salt of doxycycline is more acidic in nature, with a 1% solution in water having a pH of 2 to 3 (1). The monohydrate salt also lends itself to the formulation of a tablet dosage form which has the ability to disperse quickly in fluids.

The acidity of tetracycline and doxycycline and the rate of dissolution and release of the drug have been linked to toxic effects (1). The doxycycline monohydrate free base formulation has been found to be less irritant to the cat esophageal mucosa than the hyclate, and tablets capable of dispersing quickly are less likely than capsules to stick to esophageal mucosa.

LIPID SOLUBILITY

The molecular configuration of doxycycline gives it its optimal lipophilicity. This property is believed to be the reason for the real clinical advantages of doxycycline.

In general terms, the body is mainly water but the membranes of its cells have predominantly lipoid properties. For an orally administered drug to be absorbed and reach its target area, it must not be merely soluble in water, otherwise it will be unable to cross the lipid barriers of cell membranes. The transfer process across the gastric barrier is by passive diffusion: the molecule leaves an aqueous medium to enter the lipoid gastric epithelium; it then enters another aqueous medium on the other side. A molecule with low lipophilicity enters the epithelium very slowly -- its transfer is inefficient. A molecule with high lipophilicity quickly enters the epithelium, but finds it difficult to leave this lipoid environment - again transfer is poor. Evidently there must be a state of optimum lipophilicity that ensures the adequate transfer of a drug throughout the body.

This state appears to have been reached for the tetracyclines with doxycycline.

The relative lipoid solubilities of tetracycline analogues have been determined *in vitro* (2) by measuring the distribution of the antibiotics at equilibrium between aqueous buffer and chloroform. The relationship of distribution coefficients at pH 7.4 was, with descending lipid solubility from left to right:

doxycycline ➤ tetracycline > demeclocycline or methacycline ➤ oxytetracycline

PROTEIN BINDING AND TISSUE AFFINITY

Although protein binding within the vascular system -- to the plasma proteins -- is important pharmacokinetically, we understand little of its nature. The binding of most antibiotics to the plasma proteins is readily reversible: as unbound molecules of drug diffuse out of the blood, bound drug dissociates to replace it. It is a state of dynamic equilibrium. Doxycycline is strongly bound to the plasma proteins (see Table 1 below), therefore it is the free fraction that represents the effective concentration of the drug.

Protein binding has the effect of retaining within the blood stream a percentage of the drug in a temporary non-diffusible form. The unbound molecules are still perfectly free to diffuse into the tissues, and the concentration gradient for this diffusion is regulated by the level of unbound drug in the plasma and by the total amount present. Protein binding is thus important in controlling the rate of metabolism or distribution of a drug.

The tetracyclines as a group are also reversibly bound to tissues; doxycycline has a greater affinity than the other members, a feature that is related to its lipophilicity. Because of this binding to plasma proteins and tissues, the concentration of unbound drug may be markedly lower than either the total plasma level or the total tissue level.

CALCIUM AFFINITY

Tetracyclines combine with divalent metals, of which the one most likely to be present in large amounts is calcium. Thus the presence of calcium hinders absorption.

Table 1 summarizes the degrees of plasma protein binding and the relative calcium binding of five tetracycline analogues. This demonstrates the superiority of doxycycline.

Table 1. Comparative serum protein and calcium binding of tetracyclines in vitro (3)

Compound	Serum binding (%)†	
	Protein	Calcium
Doxycycline	82	19
Tetracycline	56	39.5
Demethylchlortetracycline	75	74.5
Methacycline	78	39.5
Oxytetracycline	35	36

† Dialysis method

STABILITY

The relative stabilities of certain tetracycline analogues in aqueous acid are:

doxycycline ➤ methacycline > oxytetracycline > tetracycline

A consequence of the greater stability of doxycycline is that unlike older forms of tetracycline it does not degrade to the nephrotoxic 'epianhydro' form which has been linked with the Fanconi syndrome.

The stability of doxycycline in alkaline solutions is comparable to that of methacycline and oxytetracycline, being similarly stabilized by the presence of complexing metal ions.

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PHARMACOKINETICS

The key property determining the pharmacokinetics of the tetracyclines, and especially doxycycline, is their lipophilic nature. This property affects all stages from absorption to excretion. Varying serum concentrations after ingestion with commercially available preparations of the same tetracycline may be related to particle form and size. The molecular configuration of doxycycline confers upon it optimum lipophilicity to enable it to be transferred through both aqueous media and lipoid cell membrane. This is considered to be responsible for the clinical benefits doxycycline possesses over the other tetracyclines, in both its pharmacokinetics and its antibacterial action.

ABSORPTION

Doxycycline is absorbed more efficiently than the other tetracyclines when taken by mouth. It is virtually completely absorbed (1,2). More than 93% of an oral dose is absorbed from the intestine which compares with figures of 30% for chlortetracycline and 66% for demethylchlortetracycline (3). Because of its optimal lipid solubility, doxycycline is rapidly absorbed from the small intestine -- 80% within one hour (1). Following an oral dose of 100 mg, therapeutic serum concentrations are reached in 30 minutes, with peak serum doxycycline values of 1.56 μg/ml attained in 90 minutes.

Effect of food, milk, and antacids

A full stomach has little overall effect on the absorption of doxycycline. This is in contrast to other tetracyclines which give depressed peak serum concentrations when taken with food. The nausea and vomiting sometimes experienced by patients who take tetracyclines when in the fasting state may thus be avoided with doxycycline.

Chelation with calcium ions in ingested food is thought to be the cause of this impaired absorption; of the tetracyclines, doxycycline has the lowest affinity for calcium ions. The decreased calcium binding, as well as rapid absorption due to high lipophilicity, explains the similar absorption patterns with doxycycline in both fasting and non-fasting studies.

It has been shown that food ingestion may slightly delay the rate of absorption of doxycycline, but does not significantly affect peak serum concentrations (4), which remain at therapeutic levels for 24 hours after administration. Milk and antacids containing aluminum, calcium, or magnesium impair absorption of doxycycline but not to the extent found with the other tetracyclines. Therefore, high milk diets and antacids should be avoided along with any of the tetracyclines. However, since doxycycline does not require frequent administration, antacid therapy can be scheduled for administration after doxycycline is almost completely absorbed -- a period of 2 hours.

SERUM LEVELS

One of the problems of prescribing antibiotics, especially to out-patients or in general practice, is that doses have to be taken at intervals throughout the day. In many cases this can lead to error (5) either through the patient missing doses or taking too many. The problem has been mainly due to the fact that sufficiently high serum and tissue levels have not been attainable with single doses because of the relatively rapid urinary excretion of most antibiotics. In contrast doxycycline gives prolonged and therapeutic serum levels after a single oral dose of either 100 or 200 mg/day (6).

Various studies have shown that oral administration of doxycycline is as efficient as intravenous administration in achieving and maintaining effective serum concentrations, and that changing from the parenteral to the oral route does not significantly affect the serum concentration. One of these (7) demonstrated that the drug is well tolerated when given intravenously, and concluded that the dosage should be the same

for both routes, namely 200 mg on the first day followed by 100 mg (or 200 mg with severe infections) every 24 hours. Using this dosage regimen, it was observed (8) that, throughout a period of 56 hours from the initial dose, the serum concentrations of doxycycline were in excess of the mean inhibitory concentration for most of the common infecting organisms (see Table 1 below).

Table 1. Serial mean serum levels after administration of doxycycline for 10 patients (8)

Dose (mg)	Hours after dose	Serum level (μg/ml)
200	1	3.32
	2	4.48
	4	3.84
	8	2.98
100	24	1.62
	32	3.20
100	48	1.34
	56	2.00

Figure 1 shows the average serum levels of doxycycline in six healthy volunteers. After a single oral dose of 200 mg, serum levels in excess of 1.0 μg/ml were still present 36 hours later.

Figure 1. Mean serum levels after a single oral dose of 200 mg doxycycline (N=6) (9)

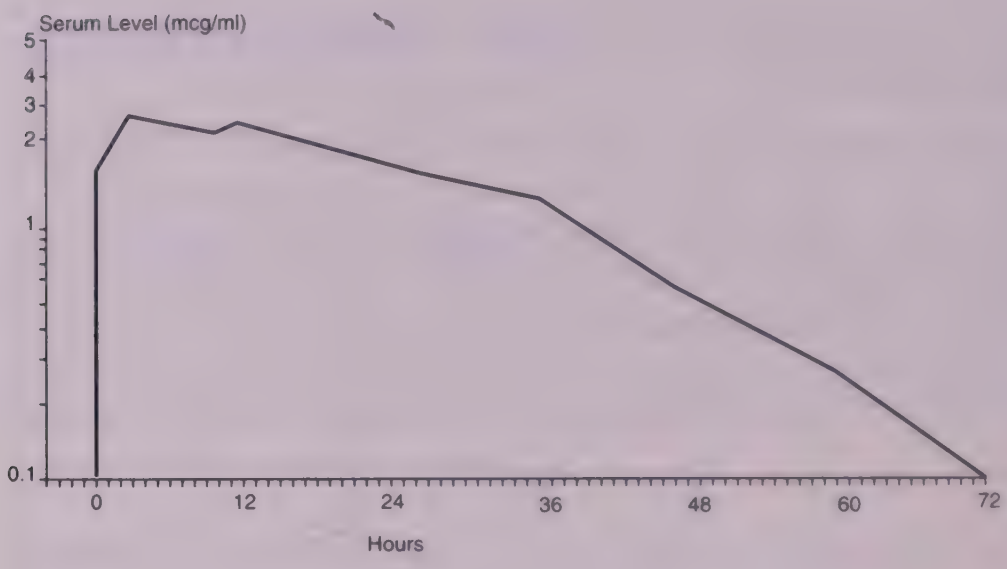
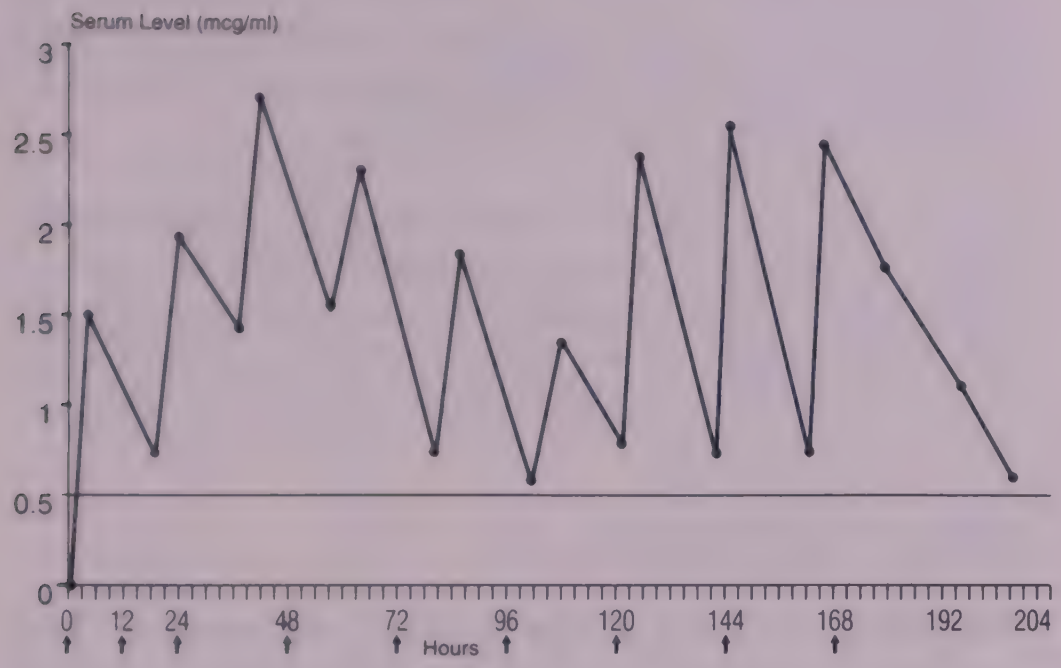


Figure 2 shows average serum levels of doxycycline found in three similar studies using the following dosage regimen: 100 mg every 12 hours for 2 doses; then 100 mg every 24 hours for 7 doses. The reference level of 0.6 μg/ml is considered as the therapeutic serum level of doxycycline based on minimum inhibitory concentrations for a variety of susceptible organisms.

Figure 2. Serum levels with multiple doses of doxycycline (6-23 volunteer subjects per data point)



This indicates that a dosage schedule of 100 mg doxycycline once a day, after the 200 mg first-day loading dose, is sufficient to maintain persistently high serum levels, above 0.6 μg/ml, with values between 0.6 and 2.5 μg/ml for approximately 36 hours after the last dose.

Serum half-life

The serum half-life (time taken for a given serum concentration to be reduced to one half its value) of doxycycline is about 15

hours for a single dose (1), compared with about 9 hours for oxytetracycline and tetracycline. With doxycycline, repeated administration increases this to about 22 hours (1). The practical significance of this prolonged half-life is that a once-a-day dose regimen is both possible and rational. This effect is the result of efficient take-up of doxycycline by the tissues which then release the drug slowly back into the bloodstream.

Doxycycline also becomes highly bound to plasma albumin whilst maintaining a dynamic equilibrium with the unbound plasma fraction. The albumin-bound fraction is biologically inert and cannot be excreted and it thus performs the function of a reservoir of antibiotic in addition to that held by the tissues.

TISSUE PENETRATION

Doxycycline has a high affinity for tissue components, a feature related to its lipophilicity. Apart from prolonging the duration of antibiotic activity, this also means that the antibiotic is concentrated and released where it is most needed, in the tissues. High levels of doxycycline are also attained in biological fluids; they, too, are related to the degree of lipid solubility and protein binding (1).

Because of this tissue binding effect, the total tissue concentration - not the free plasma concentration -- of doxycycline is the important parameter of efficacy when considering the different organ systems. Tissue concentrations above the therapeutic range have been found in the following tissues and biological fluids: testis, prostate gland and its fluid, ovary, uterus, placenta, fallopian tube, breast and breast milk, lung, bronchial wall and inflammatory bronchial secretions (non-inflammatory bronchial mucosa secretes markedly less antibiotic), paranasal sinus secretions, tonsil, lymph nodes and lymph, thyroid, stomach, omentum, liver, gall bladder, and bile. Table 2 highlights some of these:

Table 2. Doxycycline levels achieved in some body tissues and biologic fluids

Tissue	Sample (hours post-dose)	Levels	
		Tissue (μg/g)	Serum (μg/ml)
Genito-urinary tract			
Testis (10)	14-18	0.99	
Placenta (10)	16	1.34	
Ovary (10)	15-24	2.90	
Uterus (10)	15	2.96	
Prostate (11)	1.5-14	1.63	
Ovary (12)	4	2.85	4.78
Uterus (12)	5	2.24	4.78
Fallopian tube (12)	3.5	3.21	4.78
Lungs (9)	5.5-7.5	3.92	3.06
Sinus secretions (13)	1-2.5	2.84	3.46

In an evaluation of doxycycline in pelvic inflammatory disease (14), plasma, tubal, and ovarian concentrations showed therapeutic levels within a few hours of the initial 200 mg dose. Levels were still within the therapeutic range more than 24 hours after the final dose.

EXCRETION

The kidney is an important organ for the excretion of tetracyclines including doxycycline, but when renal function is impaired or absent doxycycline is alone in being excreted almost entirely through the alimentary tract. In the person with normal renal function (creatinine clearance above 75 ml/min), however, about 40% of an absorbed dose is excreted by the urine in 70-72

hours. This percentage excretion may fall as low as 1-5%/72 hours in individuals with severe renal insufficiency (creatinine clearance below 10 ml/min).

The mechanism of renal clearance appears to be glomerular filtration; but if the urine becomes acidic and the lipophilicity of doxycycline reaches a maximum, partial tubular reabsorption would seem to be a possibility.

Doxycycline is concentrated in bile but this is not an important route for elimination. Various studies have shown that the other major route of excretion is via the bowel. Doxycycline diffuses from the bloodstream into the lumen of the small intestine where it becomes bound to the contents and is excreted in the feces either as a conjugate or as a stable complex (2). In this state the drug is biologically inert, hence its virtual lack of effect on the intestinal flora.

This alternate route, with enhanced excretion through the gastrointestinal tract, has great therapeutic importance because a number of workers have demonstrated that doxycycline can be given in normal dosage to patients who are anephric or have impaired renal function. The serum half-life of the drug remains unchanged in these patients; hemodialysis has little effect on the serum concentration, and no toxic effects have been reported in this context.

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ANTIMICROBIAL ACTIVITY

BACTERIOLOGY

Doxycycline is a true broad spectrum antibiotic with a wide range of activity against both Gram-positive and Gram-negative bacteria and a variety of other micro-organisms such as rickettsiae, mycoplasmas, chlamydiae, and amebas.

When the first of the tetracyclines was discovered in 1948, the only other available antibiotics were penicillin and streptomycin, both of which had limited ranges of activity. The new antibiotic's wide range covered most of the organisms susceptible to these two and a variety of others as well. Since then, more tetracyclines have come into clinical use: on the whole, they have closely similar antimicrobial spectra. There are, however, differences in their *in vitro* activity against certain pathogenic bacteria (1,2) that make it worthwhile for bacteriology laboratories to include specific antibiotics in sensitivity tests.

Mode of action

The tetracyclines (including doxycycline) are primarily bacteriostatic (in high concentrations they are bactericidal). Thus the body depends upon its phagocytic defence mechanisms to destroy the organisms which the antibiotic has prevented from multiplying further. Tetracyclines exert this bacteriostatic effect by interference with protein synthesis, probably at the stage of formation of peptide linkages.

Drug resistance and sensitivity

Resistance of an organism to a drug may be part of nature's endowment of that organism or it may be acquired. It is acquired resistance that is of practical importance and

troublesome -- especially in a hospital environment where the opportunities for an organism to develop resistance are greater.

Organisms originally sensitive to tetracyclines develop resistance slowly and as a rule no difficulties arise during the treatment of patients with acute infections. Once an organism becomes resistant to one tetracycline it is not always resistant to others. Within recent years, pneumococci have shown a tendency to develop resistance to tetracycline, but fortunately strains of *Haemophilus influenzae* are mostly remaining sensitive -- respiratory infections with *H influenzae* are one of the more important indications for treatment with doxycycline.

For doxycycline, as for other drugs in the tetracycline class, micro-organisms may be considered highly sensitive if the minimum inhibitory concentration (MIC) is 0.5 to 2.0 μg/ml, and slightly sensitive if the MIC is 2.0 to 5.0 μg/ml.

Table 1 shows that the sensitivities of some common micro-organisms are many times higher with doxycycline than with conventional tetracycline.

Table 1. Antibiotic sensitivities of doxycycline and tetracycline (3)

Organism	Minimal Inhibitory Concentration of Antibiotic (μg/ml)	
	Doxycycline	Tetracycline
Pneumococcus	0.2	0.8
Group A streptococci	0.4	0.8
Haemophilus influenzae	1.6	1.6
Mycoplasma pneumoniae	1.6	1.6
Legionella pneumophila	1.0	5.2

Reports on patterns of resistance for 32 antibiotics (4,5), documented these to be essentially similar for both hospital in-patients and out-patients. Remarkable, however, was a

decreasing resistance not only of coagulase-positive strains of *Staphylococcus aureus* but also of other micro-organisms towards doxycycline. An expected increase in resistance towards the tetracyclines generally was shown only with some Gram-negative rods. The incidence of strains resistant to doxycycline, tetracycline, erythromycin, and cloxacillin isolated from the paediatric ward, was low. This might have been due to the limited use of these antibiotics by pediatricians.

Evidently, comparatively small changes in molecular structure may result in relatively large differences in the resistance pattern -- this was corroborated by the striking difference in resistance patterns between tetracycline and doxycycline, with doxycycline showing greater activity (4,5). This stresses the need for specific antibiotic sensitivity testing.

A disc-susceptibility test (6) demonstrated that for *S aureus* 27 out of 27 cultures were sensitive to doxycycline, and only 17 out of 27 cultures were sensitive to tetracycline.

Extensive laboratory investigations into the *in vitro* activity of doxycycline, ampicillin, cephaloridine, and co-trimoxazole, towards those micro-organisms commonly associated with disease in man showed that doxycycline has the broadest spectrum of activity of the agents examined (7).

This study (7) also examined three strains of *Mycoplasma pneumoniae* for their response to doxycycline and ampicillin. All were inhibited by 0.125 or 0.25 μg doxycycline/ml. Ampicillin was, as expected, inactive. Accordingly, it was suggested that doxycycline would be active against L-forms of bacteria as well.

In an *in vitro* susceptibility assessment of 600 strains of *H influenzae* with doxycycline (8), the level of resistance was very low (<1%); importantly, the pattern of sensitivity had not changed significantly over the earlier 10 years, suggesting the suitability of doxycycline in the management of chronic bronchitis when *H influenzae* is involved.

INTESTINAL FLORA

Doxycycline, by virtue of its physico-chemical properties, has the outstanding advantage over the other tetracyclines of not -- or hardly at all -- disturbing the normal intestinal flora. Its rapid absorption and its excretion, highly bound in a biologically inactive form to the intestinal contents, are the characteristics responsible for this desirable attribute. Just how significant, clinically, this is, can best be judged by considering the effect of other tetracyclines on the intestinal flora.

Broad spectrum antibiotics as a whole are liable to cause gastrointestinal upset when given orally. As far as tetracyclines are concerned, one of the main reasons is incomplete absorption -- and as the dose is increased, so too is the amount remaining unabsorbed. In most cases the effect is trivial, producing tolerable degrees of anorexia, nausea, loose stools, etc, and is accepted by the patient; but occasionally the effect is so severe, especially with regard to diarrhoea, that treatment has to be stopped. This is particularly the case in seriously ill and debilitated patients.

The trouble is due to 'superinfection'. Unabsorbed, biologically active antibiotic in the gut suppresses the normal flora and allows antibiotic-resistant organisms to flourish. By upsetting the natural balance, the antibiotic is responsible for unwanted gastrointestinal effects. Most of the normal flora from mouth to anus -- streptococci, coliforms, clostridia, lactobacilli -- are sensitive. They are replaced by overgrowth of one or more of four chief organisms: *Candida albicans*: this can produce oral thrush, diarrhoea, pruritus ani, etc; *Proteus* species and *Pseudomonas* species: both of these, if they gain an upper hand and are antibiotic-resistant, cause diarrhoea; *Staphylococcus aureus:* this organism is notorious for being resistant to most antibiotics and, if it is responsible for superinfection, the consequences can be most serious, especially for patients who have undergone gastric surgery. For instance, superficial necrosis of the small bowel may lead to profuse diarrhoea and death. The remedy in all cases of superinfection is to stop

treatment with the offending antibiotic and to take other measures as appropriate.

Another problem causing increasing concern is transferable drug resistance. Bacteria that have been exposed to an antibiotic and become resistant to it, can transfer this resistance (known as R factor) to other bacteria that have not been exposed to the antibiotic. And moreover, not only can they transfer it to bacteria of their own species, but to unrelated bacteria as well. Thus it is possible for a normal inhabitant of the gut to develop resistance to an antibiotic and then later to transfer this resistance to an infecting pathogen. This can give rise to serious problems.

The innocuous behavior of doxycycline towards the intestinal flora is well documented (9), with the bacterial flora of the gut not affected even with prolonged treatment on high dosage.

A study (10) compared the effects of 2 g of oral tetracycline (500 mg in 4 divided doses) per day with 200 mg of oral doxycycline (100 mg twice a day), for seven days. The results showed that doxycycline caused a decreased growth of pseudomonas, klebsiella, and staphylococci, and produced smaller increases of *Streptococcus fecalis* and candida than did tetracycline; this would indicate that intestinal side-effects are more of a problem with incompletely absorbed tetracyclines than they are with doxycycline. Three out of the 10 women receiving tetracycline suffered from diarrhoea, while none of the subjects receiving doxycycline reported this effect.

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CLINICAL EXPERIENCE

Doxycycline has proved itself effective against a wide range of infections due to susceptible strains of both Gram-positive and Gram-negative bacteria as well as those due to other micro-organisms. However, strains of some bacteria have been found resistant to the tetracyclines. Therefore, culture and sensitivity testing can be helpful to determine the susceptibility of the infecting organisms to doxycycline. However, despite its desirability, bacteriological help is often impractical at the bedside and clinical judgement remains of first importance. Respiratory infections, both of the upper and lower tract, and sexually transmitted diseases (STDs) are particularly amenable to treatment with doxycycline -- indeed, many authors regard this drug as the antibiotic of first choice in these conditions.

In the following pages, clinical experience with doxycycline is outlined according to system or specialty, as appropriate. Respiratory infections and STDs are described in separate sections.

EAR, NOSE, AND THROAT INFECTIONS

Infection of ear, nose, and throat are amongst the most common conditions for which doxycycline is prescribed. The efficacy of doxycycline is based on a number of distinctive features of its pharmacokinetics and activity.

There is rapid and complete absorption after oral ingestion, leading to high serum levels from the start of treatment. The antibiotic penetrates into tissues and secretions in concentrations which are likely to be biologically active. Doxycycline has an extensive spectrum of antibacterial activity against common pathogens infecting tissues of the ear, nose and throat, including *Haemophilus influenzae*, *Diplococcus pneumoniae*, and

Mycoplasma pneumoniae. It is excellently tolerated, so that patients are more readily inclined to take the antibiotic as prescribed, and treatment is rarely interrupted by side effects.

Tissue levels of doxycycline measured in the human tonsil were between 2.50 and 5.60 μg/g one hour after the last administration, and between 1.56 and 4.30 μg/g after 24 hours (1).

In treating chronic bronchitis, attention should be paid to possible reservoirs of infection such as sinuses when selecting an antibiotic. In a double-blind trial (2) comparing doxycycline (200 mg on the first day followed by 100 mg OD for 7 days) with ampicillin (250 mg QID for 7 days) in 44 cases of acute and chronic sinusitis showed significantly superior results with doxycycline: 90% responded to doxycycline and 35% to ampicillin.

Infections refractory to other antibiotics sometimes respond satisfactorily to doxycycline. Fifteen of 16 patients previously given penicillin were successfully treated with doxycycline (3). In 49 patients treated with doxycycline for a wide variety of infections (4), from which coagulase positive *Staphylococcus aureus*, *Diplococcus pneumoniae*, and ∝-hemolytic streptococcus were among the organisms cultured, good responses were observed in 38 patients, fair in 5, and poor-to-fair in 6. Among these were 20 patients who had not responded to chloramphenicol, ampicillin, lincomycin, or erythromycin, and 17 of them obtained a satisfactory clinical result with doxycycline treatment.

Twelve patients suffering from purulent maxillary sinusitis and treated with doxycycline 200 mg daily were all bacteriologically cleared by the sixth day (5). Sinus secretions were obtained by cannula and simultaneous blood samples were taken for serum estimations. The concentrations of doxycycline in the sinus secretions were in the region of 0.5-7.5 μg/ml which were 10 times higher than the MIC values for the pathogens (mainly pneumococci, but also *Staph aureus*, streptococci, and *Haemophilus influenzae)* originally isolated from the secretions.

This work showed that doxycycline penetrated sinus secretions even under severe inflammatory conditions.

In another series (6), bacterial studies were performed for sensitivity to doxycycline in 45 patients with acute tonsillitis. The age of the patients ranged between 18 and 24 years. The most frequently isolated organisms were *Staphylococcus aureus*, β-hemolytic streptococci, and *Streptococcus viridans*. Twenty-eight of the 32 coagulase positive staphylococci were sensitive and 4 strains were not. Twenty-seven of these patients showed an excellent response to doxycycline therapy. Overall, the results were considered to be excellent in 40 patients and poor in five (including the four from whom resistant strains of staphylococci were isolated).

SKIN INFECTIONS

Doxycycline has attracted interest for use in dermatology as an antibiotic with particularly favorable attributes. It has an appropriate wide spectrum of antibacterial activity and gives excellent penetration of the tissues -- of special importance when infected varicose ulcers with deep-seated pathogens are to be treated. High tissue levels are maintained on a once-daily low dosage regimen, and there is a low incidence of generally mild side effects even during long-term therapy. This is particularly useful in cases of acne vulgaris and studies (7) have shown the effectiveness of doxycycline in this condition.

Several authors have substantiated the usefulness of doxycycline in skin infections of bacterial origin. One evaluation (8) used the antibiotic in the treatment of 62 patients with various dermatoses, including abscesses and carbuncles. A decidedly favorable response was obtained in 55 and an adequate response in the remaining 7. Doxycycline was also tried in 35 patients with pyogenic infections of the skin (9). The clinical effectiveness of the drug was evident in a single daily dose of 3 mg/kg body weight and it was well tolerated. All strains of *Staphylococcus aureus* and β-hemolytic streptococcus were sensitive to the drug in low concentrations.

Doxycycline is of particular value in infected, recalcitrant ulcers, such as varicose ulcers of the legs. In these cases the offending organism is deeply seated and cannot be reached by topical medication; prolonged and effective tissue levels of antibiotic (as given by doxycycline) are needed for their control.

There is the possibility of side-effects such as photosensitivity with systemic treatment for chronic skin infections. Fortunately, photosensitivity has never been shown to be a complication of treatment with doxycycline, though it is not unknown with other tetracyclines.

URINARY TRACT INFECTIONS

Two bacterial species are commonly implicated in acute infections of the urinary tract -- *Escherichia coli* (80% of cases) and Proteus species (10% of cases). Most cases respond well to antibiotic therapy (10), and doxycycline has proved an efficacious antibiotic primarily because of its broad antibacterial spectrum.

Almost by definition, chronic urinary tract infections imply resistance to antibiotic therapy. Predominant organisms are *Escherichia coli*, *Pseudomonas* species and *Klebsiella* species, and frequently more than one organism is present. Doxycycline compares favorably with other antibacterials used in treatment (11), again because of its broad antibacterial spectrum.

Urinary concentrations of doxycycline are very much higher than the MICs of most organisms and suggest that doxycycline would be effective therapy for urinary tract infections by susceptible organisms (12).

Of particular importance in the treatment of urinary tract infections is an absence of harmful effects on renal function and a lack of accumulation of the drug in patients with renal failure. In both these respects doxycycline is an ideal antibiotic.

In the treatment of bacterial and mycoplasmal prostatitis doxycycline has proved especially valuable because of its high degree of penetration into the tissues. The concentration of doxycycline in the prostatic tissue was a mean of 2.75 μg/g, with a maximum of 4.81 μg/g (13). These findings suggest a tendency for doxycycline to accumulate in prostatic tissue, and as there are only a few antibiotics that penetrate into the prostate, the importance of this drug in prostatitis is obvious (14).

GASTROINTESTINAL AND HEPATO-BILIARY INFECTIONS

Doxycycline is a most useful antibiotic for the treatment of infections in the gastrointestinal tract and hepato-biliary system because it is rapidly absorbed, even in the presence of food, and is active against the pathogens commonly encountered in the gut and biliary tract. Its high lipophilicity encourages efficient transport across cell membranes and sustained high antibiotic levels in intestinal mucosa and bile -- important factors in treating infections of the gastrointestinal tract (15). Doxycycline is unlikely to affect normal bowel flora; by the time the drug reaches the large intestine it has become biologically inactivated.

In 15 patients suffering from predominantly amebic colitis, and treated with doxycycline, improvement was noted in all, with clinical and parasitological cure within 12 days in 11 cases (16).

Conservative treatment of inflammatory conditions of the biliary tract, frequently delays, and may remove, the necessity for surgical intervention. This is particularly important in the elderly or where pre-existing cardiovascular or pulmonary conditions may impose an additional risk to operation. Adequate antibiotic management may gain valuable time in these situations. Doxycycline achieves effective levels in the bile, has shown no evidence of inducing liver damage, and has been used successfully in cases of acute and chronic cholecystitis (17).

OPHTHALMOLOGIC INFECTIONS

The use of doxycycline in ophthalmology is based principally on the observations that doxycycline satisfactorily penetrates the aqueous humor and other ocular tissues, and that it is active against organisms, including chlamydiae, which affect the eye. This is ascribed to the high lipophilicity of doxycycline in spite of high protein binding.

A significant finding was that the concentration of doxycycline in the aqueous humor of eyes with inflamed anterior segments is almost double that in normal eyes, being much higher than the minimal inhibitory concentrations at least for the Gram-positive micro-organisms (18).

Doxycycline has been used in a variety of ophthalmological infections including acute conjunctivitis and acute dacryocystitis with satisfactory results (19). However, the most promising application in this specialty would seem to be in the mass treatment of trachoma where the simplicity of once-daily administration is a great advantage (20).

OBSTETRIC AND GYNECOLOGIC INFECTIONS

Obstetric and gynecologic infections are often multimicrobial, and anaerobic pathogens are relatively common. There is thus a place for truly broad spectrum antibiotic therapy in practice. Among the characteristics of doxycycline are several which offer important practical benefits in therapy.

Doxycycline has a high degree of efficacy against the many Gram-positive organisms commonly implicated, and also against bacteroides, clostridia, and other Gram-negative bacteria sometimes involved. Its rapid absorption and excellent penetration into the tissues of the female genital tract are reflected in the generally satisfactory nature of the clinical results. A further finding in favor of doxycycline was that this antibiotic had no appreciable effect on Doderlein's bacillus in the vagina -- other antibiotics, such as penicillin, reduced the

concentration of this organism and so disturbed the natural balance of the flora.

Doxycycline has been used in a variety of gynecologic and obstetric infections including salpingitis (non-specific, gonococcal, post-operative), endometritis (post-abortion, puerperal), parametritis, pelvic abscess, Bartholinitis, infected wounds and episiotomies, and post-operative cystitis (21).

In an *in vitro* study of anaerobic bacteria from the female genital tract, doxycycline, at 5μg/ml, was effective against 81% of 231 anaerobic isolates (22); 79-80% of *Bacteroides fragilis* strains and 96% of Clostridium strains were inhibited at this concentration.

Doxycycline has been used to treat coincidental infections with susceptible organisms during the early part of pregnancy. However, it should be avoided during the second half as the drug crosses the placental barrier and may damage the teeth of the developing foetus. Doxycycline is also secreted in the milk of lactating women receiving the antibiotic.

IN SURGICAL PRACTICE

In the context of surgery, two qualities of doxycycline appear of particular value. The broad antibacterial spectrum of doxycycline includes activity against *Staphylococcus aureus* and *Streptococcus haemolyticus* (23) -- both commonly implicated in surgical infections. In addition, doxycycline is well tolerated, so that after surgery, debilitated patients are rarely subjected to the additional stress of drug side effects. It is noteworthy that, with doxycycline, gastrointestinal side effects are uncommon because it is biologically inactivated before it reaches the colon.

Antibiotics have an important role to play in surgical practice, and are used for one or more of six basic reasons. First, they may be given to resolve a potential 'surgical' infection so that the patient no longer requires surgical intervention. Second, they may be used as therapy supplementary to surgery. Third,

they may be used in order to clear before operation an infection associated with the surgical condition. Fourth, they may be used to treat an infection not associated with the surgical condition so that the patient comes to the operation in the best possible state. Fifth, they may be used to treat postoperative infection. Sixth, they may be used to prevent postoperative infection in patients known to be susceptible. Broad spectrum antibiotics find an extensive use in surgical practice because of the wide variety of infections encountered.

One study (23) reports on the use of doxycycline in 117 cases of abscesses, cellulitis, infected wounds, infected burns, peritonitis, paronychia, and appendicitis. Employing also the normal concurrent therapy for the infection (local care and/or incision and drainage, etc) a favorable response was obtained in 113 of the infections. Thirteen bacterial isolates were identified, and excellent results were gained with *Escherichia coli* infections as well as those with *Staph.aureus* and *Strep. haemolyticus*.

In some instances, a comparison was possible between doxycycline and other previously used antibiotics (including penicillin, streptomycin, and chloramphenicol). In 25 out of 33 (76%) infections showed a better response to doxycycline than to earlier antibiotics.

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RESPIRATORY TRACT INFECTIONS

A major indication for doxycycline therapy is respiratory infection. Two conditions prevalent in many countries are acute bronchitis and the acute exacerbations of chronic bronchitis, a fact brought out strongly by the results of a multi-country trial (1) in which these two conditions accounted for 44.2% of the patients treated.

A measure of the value of doxycycline in respiratory infections may be gained by considering the results of the large clinical study referred to above (1). In all, 3,572 patients were treated, mostly by their general practitioners. Commonest diagnoses were acute bronchitis, acute exacerbations of chronic bronchitis, and tonsillitis, but the total range of conditions treated was wide. Most patients became afebrile in two to three days after commencement of doxycycline therapy; volume and viscosity of sputum diminished, and by the end of three weeks most (83%) of the patients who had presented with cough were no longer troubled by this symptom. Pain and inflammatory symptoms also resolved. Overall, 87% of patients showed 'very good' or 'good' results.

In 20 patients of recurrent sinusitis and chronic pulmonary disease (sinobronchial syndrome), doxycycline 100 mg b.i.d. was administered for 10 days; 85% had complete resolution of clinical signs and symptoms within 48 hours of initiation of therapy (2). The remaining also responded by the end of the treatment period. Of the micro-organisms cultured from patients, which included *Staphylococcus aureus* and *Klebsiella pneumoniae*, most were sensitive to doxycycline.

Chronic bronchitis itself is increasing in prevalence. Acute exacerbations are common in winter and are particularly liable to be serious for the elderly. Doxycycline is very often effective against *Haemophilus influenzae* and *Diplococcus pneumoniae* --

the two organisms most commonly implicated in chronic bronchitis -- so it is an antibiotic of choice for acute exacerbations of this condition. It is also indicated in acute bronchitis, pneumonia, bronchopneumonia, and bronchiectasis when the organisms are known or are considered to be sensitive.

In the treatment of chronic and recurrent lung infections it has been shown that doxycycline was an effective alternative to conventional forms of treatment with specific advantages -- including once-daily dosage -- over tetracycline and ampicillin (3).

Doxycycline has an important role in pneumonia (especially atypical pneumonia) because of the frequency with which *Mycoplasma pneumoniae* is responsible (4). In fact, some workers believe that doxycycline should be the first-choice antibiotic in pneumonia.

A recent report indicates that *Streptococcus pneumoniae* accounts for 25-60% of out-patient acquired pneumonia, and *M pneumoniae* accounts for as much as one third of pneumonia in young adults (5). This organism is also reported to be involved in 6-59% cases of pharyngitis, in 12% cases of otitis, and in 25% cases of upper respiratory illnesses (6). Cultures of *M pneumoniae* and serologic diagnosis are not readily available in most clinical laboratories, making empiric treatment with doxycycline, which effectively covers the microbe, a good first-choice in respiratory infections.

In 10 cases of confirmed mycoplasma pneumonia in which the therapeutic results were excellent, the temperatures returned to normal in one-and-a-half days and the radiological pictures in one to two weeks (7).

Bronchopneumonia complicating type A influenza has also responded satisfactorily to treatment with doxycycline (7). In 15 patients with acute suppurative bronchopneumonia treated with the usual dosage regimen of doxycycline (8), with no other drug or treatment given, all showed marked improvement in terms of cough, temperature, and quantity and quality of sputum.

Biochemical analyses revealed no hepatic or renal impairment, though two patients complained of minor gastro-intestinal upsets.

Lung abscess and bronchiectasis have also responded well to treatment with doxycycline, as has acute bronchitis. In 24 patients treated with doxycycline for acute bronchitis, all responded and became afebrile in an average of 18 hours (9). All strains of bacteria isolated were sensitive except for one variety of pseudomonas.

The comparative efficacy of doxycycline versus amoxicillin, cephalexin, cefaclor, and enoxacin was examined in cross-over and blinded studies of acute bacterial exacerbations in chronic bronchitis and asthma (10). Except for cefaclor, all the agents effectively controlled the acute infection. The doxycycline-treated patients, however, had longer infection-free periods, being 25% longer than amoxicillin, 333% longer than cephalexin, 233% longer than cefaclor, and 75% longer than enoxacin. Doxycycline evidently demonstrated a superior ability to provide a longer period of suppression of the latent bacterial bronchial flora than any of the other antibacterials, extending up to a mean of 166 days in some groups.

The convenience of doxycycline's once-daily dosage regimen and the fact that it is generally well tolerated naturally combine to recommend this antibiotic for use either as a prophylactic in chronic bronchitis or for treatment of acute exacerbations in chronic bronchitis.

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SEXUALLY TRANSMITTED DISEASES

The past two decades have witnessed dramatic changes in the pattern of sexually transmitted diseases (STDs). Before the early 1970s, the major bacterial STDs were syphilis and gonorrhea. Then, in the mid to late 1970s, a strain of *Chlamydia trachomatis* began to emerge as an important infectious agent. As the rates of syphilis and gonorrhea declined, the rates of genital chlamydial infections increased precipitously.

Today, infections caused by *C trachomatis* have reached epidemic proportions throughout the world. The World Health Organization (WHO) estimates an incidence of 10 million per year in Europe alone (1). *C trachomatis* infections have placed a heavy toll on women, in whom they are currently the major cause of pelvic inflammatory disease (PID) and resultant infertility or ectopic pregnancy. The public health implications of these sequelae are so enormous that the WHO has recently called for strong measures to curb the threat of genital chlamydial infections (1).

Tetracyclines have a long history of use in a variety of STDs, and are one of the few classes of antibacterial agents with predictable efficacy against chlamydial organisms (2,3). Doxycycline is usually recommended because it offers, in addition to high antichlamydial activity, greater efficacy against other bacterial STD pathogens, convenient b.i.d. dosage, lower incidence of side effects, and it is devoid of the ototoxicity inherent with minocycline.

This section presents an update on the epidemiology of STDs and the role of doxycycline in the treatment of both classic and more recently recognized infections.

ANTIBIOTIC SUSCEPTIBILITY OF CAUSATIVE ORGANISMS

Classic STDs

Resistance of *Neisseria gonorrhoeae* to penicillin began in the 1970s and is now so widespread that the drug is used only in restricted geographical areas (4). In recent years, tetracycline resistance has also become problematic (5). Both the WHO and the Centers for Disease Control (CDC) recommend use of doxycycline in patients with gonorrhea because of the frequent coexistence of gonorrhea and chlamydial infections (1,6).

Penicillin and tetracycline are not the only antibiotics associated with *N gonorrhoeae* resistance. Recently, strains resistant to some cephalosporins, spectinomycin, and erythromycin, have also been reported (4,5). Even newer quinolone regimens have become unreliable in some areas (7). At present, the third-generation cephalosporin, ceftriaxone, appears to be the most active antibiotic against *N gonorrhoeae,* but strains with decreased susceptibility have already been isolated (5).

Treponema pallidum, the spirochete causing syphilis, remains highly susceptible to both penicillin and tetracyclines (8,9). While few *in vitro* susceptibility studies have been conducted, there are no reported cases of therapeutic failure with use of doxycycline, despite years of widespread use (9).

The *C trachomatis* serotype responsible for lymphogranuloma venereum and *Calymmatobacterium granulomatis,* the cause of granuloma inguinale, are both highly susceptible to tetracyclines (10). Doxycycline is usually preferred in these infections because of its superior tissue penetration (8,11). Although *C granulomatis* is susceptible to trimethoprim/sulfamethoxazole, the spectrum of penicillin and erythromycin does not include this intracellular pathogen. In recent years, there have been reports (12,13) of tetracycline and sulfonamide-resistant strains of *Haemophilus ducreyi*, the cause of chancroid. Nevertheless, doxycycline is still being successfully used to treat chancroid in many areas.

Tetracyclines and rifampin display the highest *in vitro* activity against all strains of the *C trachomatis* serotype responsible for the current chlamydial epidemic (3). Doxycycline is generally considered the tetracycline of choice in these infections, especially when PID is suspected (6,14,15). Erythromycin is also active, but this drug and other alternatives such as sulfonamides, clindamycin, and quinolones, such as ofloxacin and ciprofloxacin, are less effective than tetracyclines, both *in vitro* and clinically (2,16).

Doxycycline is the most frequently used empiric agent in nongonococcal urethritis in men because it is effective against the mycoplasmal organism *Ureaplasma urealyticum*, which ranks behind *C trachomatis* as a causative agent in this infection (2). A recent *in vitro* study of 35 *U urealyticum* strains isolated from men with nongonococcal urethritis revealed that doxycycline was the most active of six antibiotics tested (Table 1). All strains were sensitive to doxycycline, while 12 strains were resistant to minocycline, 34 to tetracycline, and 27 to erythromycin (17).

Table 2. Antibiotic susceptibility of 35 low-passage Ureaplasma urealyticum strains isolated from patients with nongonococcal urethritis (17)

Antibiotic	Concentration* (μg/mL)	Sensitive	Intermediate†	Resistant
Minocycline	1	18	5	12
Doxycycline	1	35	0	0
Demeclocycline	1	20	4	11
Tetracycline	1	1	0	34
Erythromycin	3	4	4	27
Lincomycin	10	3	0	32

* Final concentration in broth containing disk.
† Broth color change not fully expressed at six days.

ROLE OF DOXYCYCLINE

Unlike most antibiotics used in STDs, the broad spectrum of doxycycline includes both classic and newer pathogens. This feature, combined with unsurpassed activity against *C trachomatis*, excellent penetration into genital tissues, and relative safety, makes it a logical choice for many venereal infections. The following indications and recommended dosages for doxycycline are derived primarily from the 1989 WHO and/or CDC guidelines (1,6,18).

Nongonococcal urethritis and/or Cervicitis

Because of high activity against chlamydial and other causative pathogens, doxycycline is the treatment of first choice for nongonococcal urethritis and cervicitis. In uncomplicated urethritis, or in proctitis, dosage is 100 mg twice daily for 7 days. The WHO recommends a longer doxycycline regimen in cervicitis, 100 mg twice daily for at least 14 days, because of the prevalence of silent PID in women with chlamydial infections. This regimen is also recommended for conjunctivitis and in sexually active heterosexual men with epididymitis.

Gonorrhea/Syphilis

Doxycycline (300 mg daily, in divided doses, for at least 10 days) is an alternative in penicillin-allergic patients with syphilis, provided that neurosyphilis has been excluded (19). Ceftriaxone is the drug of first choice in uncomplicated gonorrhea; in penicillin-allergic patients, doxycycline is a possible alternative. Because of the high likelihood of concurrent chlamydial infection, both the CDC and the WHO advise that treatment of gonorrhea include doxycycline. Dosage of doxycycline in such combined treatment programs is the same as in nongonococcal urethritis/cervicitis.

Postgonococcal urethritis

Since unsuspected concurrent chlamydial infection is the most frequent cause of urethritis following treatment of gonorrhea

alone, doxycycline is recommended for this condition. In addition, doxycycline is active against *U urealyticum*. Doxycycline is also recommended in patients who experience relapse following treatment of nongonococcal urethritis with erythromycin because it is more active than erythromycin against *C trachomatis* and *U urealyticum* (7).

PID

Most cases of acute PID in sexually active females are caused by *C trachomatis* or *N gonorrhoeae*; facultative and anaerobic bacteria may also be involved, and several pathogens may be present simultaneously. *Mycoplasma hominis* and *U urealyticum* have been isolated in up to 86% of cases with PID (20). Thus, optimal treatment consists of a combination of antibiotics active against all these potential pathogens.

In outpatient treatment, the current CDC recommendations include ceftriaxone (250 mg IM once) followed by oral doxycycline (100 mg b.i.d.) for 14 days. All PID patients treated on an outpatient basis should be re-evaluated in three days and hospitalized if there is no improvement.

For hospitalized patients, the PID regimen includes cephalosporins, or other suitable parenteral antibiotics, which provide adequate coverage against gonococci and other gram-negative aerobic and anaerobic organisms. After hospital discharge, doxycycline 100 mg oral b.i.d. is continued to a total of 10 to 14 days of treatment.

Lymphogranuloma venereum/Granuloma inguinale

Recommended dosage of doxycycline in lymphogranuloma venereum is 100 mg orally twice daily for 21 days. In pregnant patients, oral erythromycin, 500 mg q.i.d. for 21 days, is the alternative. In granuloma inguinale, the doxycycline dosage is 100 mg b.i.d. until healing of lesions, which may require 2 to 5 weeks. The alternative to tetracyclines is trimethroprim / sulfamethoxazole (6).

SEXUAL PARTNERS

Sexual partners of patients with any form of chlamydial infection should be treated presumptively, regardless of negative findings on examination or diagnostic tests. Because *C trachomatis* infections are so often mild or asymptomatic, the WHO advises an active search for infection in high-risk groups, most notably, sexually active young people under 25, including pregnant women and attendees of STD clinics, family planning clinics, and youth health centers.

RECENT COMPARATIVE CLINICAL STUDIES

Several recent trials have compared the doxycycline regimens recommended by the WHO or the CDC with potential new regimens for nongonococcal urethritis and/or cervicitis. Most of these regimens have proved less effective and none has proved more effective than doxycycline regimens.

For example, a randomized, double-blind trial (21) compared two 7-day regimens of ciprofloxacin (750 mg and 1000 mg twice daily) with doxycycline (100 mg twice daily) in 178 men with nongonococcal urethritis. At both 2 and 4 weeks after therapy, overall clinical response was comparable in all treatment groups. However, among patients who initially had chlamydia-positive cultures, the identical *C trachomatis* strain was re-isolated within 4 weeks after treatment in 52% of 21 patients treated with 750 mg ciprofloxacin and in 38% of 16 treated with 1000 mg ciprofloxacin. In contrast, cultures remained negative in all 10 doxycycline-treated patients who were originally culture positive. The authors concluded that ciprofloxacin is inadequate for treatment of chlamydial urethritis in men due to the high relapse rate.

Two prospective, randomized studies comparing 7-days treatment courses with ofloxacin versus doxycycline suggest that this quinolone is also associated with relapses. One trial (22) compared ofloxacin (300 mg b.i.d.) with doxycycline (100 mg b.i.d.) in 92 males and females with nongonococcal urethritis

and/or cervicitis. Although the two regimens had comparable microbiological and clinical response rates for chlamydial infections, the recurrence rate in infections due to *U urealyticum* was higher in the ofloxacin group.

The second study (23) compared doxycycline (100 mg b.i.d.) with ofloxacin (300 mg b.i.d.) in 114 men with uncomplicated urethritis due to either *N gonorrhoeae* or *C trachomatis*. In patients with gonorrhea, all 30 in the ofloxacin group became culture negative compared with 32 of 34 patients treated with doxycycline. In patients with *C trachomatis* infection, all 10 treated with doxycycline displayed microbiologic cure while 3 of 18 patients treated with ofloxacin were microbiologic failures. The investigators concluded that ofloxacin is effective treatment for uncomplicated urethritis in men but may not reliably cure chlamydial infections.

Despite the availability of numerous new antibiotics, doxycycline continues to play an important role in the treatment of a variety of STDs. The second-generation tetracycline is a drug of choice against all types of chlamydial infections as well as infection with other pathogens, such as *U urealyticum*. The efficacy of doxycycline is excellent in nongonococcal urethritis, cervicitis, and PID.

The role of doxycycline in classic STDs has changed little, despite years of widespread use. Although microbial resistance has reduced the usefulness of tetracyclines in gonorrhea and chancroid, doxycycline remains the agent of choice in the treatment of lymphogranuloma venereum and granuloma inguinale and is still recommended as an alternative to penicillin in syphilis.

In their guidelines for treatment, the WHO and the CDC considered convenience, patient tolerance, and side-effect potential as well as efficacy. In this regard, doxycycline's long history of efficacy plus good toleration and convenient b.i.d. dosage, has made it an excellent antibiotic for today's STDs.

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TOLERATION PROFILE

SIDE EFFECTS

In clinical efficacy studies doxycycline was generally well tolerated. Due to its virtually complete absorption, side effects of the lower bowel, particularly diarrhea, have been infrequent. An analysis of cumulative studies shows the side effect rate with doxycycline to be less than 1% for any one side effect, except nausea which is a little below 2%. This tendency to nausea can be reduced by administering doxycycline with meals as its absorption is largely unaffected by concomitant food or milk.

Clinical data on side effects culled from a very large, multi-country study with doxycycline in 3,572 patients with respiratory tract infections (1) is representative of the good toleration of the drug (see Table 1).

Table 1. The number and percentage of side-effects recorded in a large multi-center trial with doxycycline in respiratory tract infections (1)

Side-effect	Number of patients	%
Anorexia	12	0.30
Frequent voluminous stool	2	0.06
Diarrhea	19	0.50
Nausea, retching	57	1.60
Intestinal spasms, meteorism	6	0.17
Heartburn, pressure over the stomach	31	0.87
Gastritis	4	0.11
Vomiting	21	0.59
Allergic symptoms of the skin (exanthems, erythema, urticaria)	9	0.25
Pruritus, itching of the skin	4	0.11
Glossitis, stomatitis	1	0.03
Anorectal complaints (vaginitis, pruritus vulvae)	1	0.03
Headache	5	0.14
Dizziness	3	0.08
Other	4	0.14
None	3392	95.00

The Prescribing Information on VIBAZINE DT at the end of this monograph elaborates on the undesirable effects which can be associated with its use.

The monohydrate benefit

The monohydrate salt of doxycycline, being less acidic in nature than the hyclate, offers a lower potential for gastrointestinal irritation. In addition, the doxycycline monohydrate tablet disperses quickly in fluids and is less likely than capsules to stick to the esophageal mucosa. Animal experiments have corroborated that the doxycycline monohydrate free base formulation is less toxic to the esophageal mucosa than the hyclate (2).

Diarrhea

Diarrhea produced by the administration of antibiotics is probably the result of an alteration in the intestinal flora. Since doxycycline is virtually completely absorbed, significantly less of the biologically active material is present in the gastrointestinal tract than with other tetracyclines. For this reason one would predict that doxycycline should be associated with less of an effect on fecal flora and less resulting diarrhea.

Furthermore, the doxycycline re-excreted back into the intestine is tightly bound to fecal contents, and in this inactivated form would also not affect the intestinal flora.

The administration of tetracycline HCl 1 g/day was observed to be associated with a significant increase in the numbers of *Proteus*, *Pseudomonas*, *Klebsiella*, fecal streptococci, and *Candida* species isolated, and with a decrease in the number of *Escherichia coli* (3). Doxycycline in a standard dose of 100 mg daily produced no significant observable population effect.

HEPATOTOXICITY

Because of its long half-life, the question of hepatotoxicity following doxycycline administration has been examined by many investigators. Toxicity from tetracyclines is the result of:

1. High levels being administered intravenously, and/or
2. A build-up of tetracycline levels in patients with renal insufficiency.

Doxycycline is normally given in smaller doses than the other tetracyclines (100 mg after the first day versus 500 mg to 2 gm daily). After oral or even intravenous administration, the levels of doxycycline never reach those attained by intravenous infusion of large doses of tetracyclines. Therefore, we would not expect hepatotoxicity to occur if the dosage given is not enough to produce blood levels sufficient for hepatotoxic effects. Also, because doxycycline has been shown not to accumulate in

patients with renal insufficiency, we would not expect to see the accumulation to hepatotoxic levels with either oral or intravenous administration.

IN RENAL INSUFFICIENCY

Caution is required when broad-spectrum antibiotics such as tetracyclines are prescribed in the presence of renal insufficiency, because their excretion through the kidneys may exacerbate the renal condition; if given in unmodified dosage, these may accumulate and can have toxic effects. The tetracyclines, with the exception of doxycycline, have been shown to be toxic in the presence of renal insufficiency (4).

This is of paramount importance in the treatment of infectious disease in patients with impaired renal function as doxycycline does not depress renal function, does not accumulate in the serum or tissues, and can, therefore, be given at normal dosage.

Observations (5) that the plasma concentrations of doxycycline are largely independent of renal function, and that an adjustment of dosage for uremic patients is unnecessary, was a major therapeutic advance. Their work has since been abundantly confirmed.

There is no significant difference in the serum half-life of doxycycline in individuals with normal and those with severely impaired renal function. Little variation was found in doxycycline serum levels with 200 mg of the drug orally in normal patients and in those with renal insufficiency (creatinine clearance between 2 and 33 ml/min; normal >75 ml/min) (6). Hemodialysis does not affect the serum half-life (7), and the drug has been shown not to accumulate in anephric patients even after prolonged periods of up to 49 days (8).

As a group, tetracyclines have an antianabolic effect which may cause a rise in blood urea nitrogen (BUN) in patients with impaired renal function. In those patients treated with doxycycline, however, no significant rise in BUN has been demonstrated (9).

Doxycycline is excreted only in part by the kidney. Most of the highly lipid-soluble drug diffuses from the blood into the lumen of the small intestine, where it was bound in an inactive form to the intestinal contents and excreted in the faeces. This is the route that takes over the burden of excretion in patients with renal failure.

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PRESCRIBING INFORMATION

VIBAZINE® DT Tablets
(Doxycycline monohydrate)

1. QUALITATIVE AND QUANTITATIVE COMPOSITION

VIBAZINE DT Tablets 100 mg:
Each tablet contains doxycycline monohydrate equivalent to anhydrous doxycycline 100 mg

2. CLINICAL PARTICULARS

2.1 Therapeutic Indications

VIBAZINE DT brand of doxycycline, a broad-spectrum antibiotic synthetically derived from oxytetracycline, is indicated in infections caused by the following microorganisms:

Rickettsiae (Rocky Mountain spotted fever, typhus fever and the typhus group, Q fever, rickettsialpox, and tick fevers)

Mycoplasma pneumoniae (PPLO, Eaton Agent)

Chlamydia psittaci (formerly agents of psittacosis and ornithosis)

Chlamydia trachomatis (formerly agents of lymphogranuloma venereum)

VIBAZINE DT is indicated for the treatment of uncomplicated urethral, endocervical, or rectal infections in adults caused by *Chlamydia trachomatis*

Calymmatobacterium (Donovania) granulomatis (formerly agents of granuloma inguinale)

Borrelia recurrentis and *B. duttonii*: the spirochetal agent of louse and tick-borne relapsing fevers

Ureaplasma urealyticum (T-mycoplasma), as an agent of nongonococcal urethritis and in males associated with infertility

Plasmodium falciparum (chloroquine-resistant falciparum malaria)

The following gram-negative microorganisms:

Haemophilus ducreyi (chancroid)

Yersinia pestis (formerly *Pasteurella pestis*)

Francisella tularensis (formerly *Pasteurella tularensis*)

Bartonella bacilliformis

Bacteroides species

Fusobacterium species

Campylobacter fetus (formerly *Vibrio fetus*)

Brucella species (in conjunction with streptomycin)

Because many strains of the following groups of microorganisms have been shown to be resistant to tetracyclines, culture and susceptibility testing are recommended.

VIBAZINE DT is indicated for treatment of infections caused by the following gram-negative microorganisms, when bacteriologic testing indicates appropriate susceptibility to the drug:

Neisseria gonorrhoeae

Vibrio cholerae (formerly *Vibrio comma*)

Escherichia coli

Enterobacter aerogenes

Shigella species

Acinetobacter species (formerly *Mima* species and *Herellea* species)

Haemophilus influenzae (respiratory infections)

Klebsiella species (respiratory and urinary infections)

Branhamella catarrhalis

VIBAZINE DT is indicated for treatment of infections caused by the following gram-positive microorganisms when bacteriologic testing indicates appropriate susceptibility to the drug:

Streptococcus species: A certain percentage of strains of *Streptococcus pyogenes* and *Streptococcus faecalis* have been found to be resistant to tetracycline drugs. Therefore, tetracyclines should not be used for streptococcal

disease unless the organism has been demonstrated to be sensitive.

For upper respiratory infections due to group A beta-hemolytic *streptococci*, penicillin is the usual drug of choice, including prophylaxis of rheumatic fever.

Streptococcus pneumoniae (formerly *Diplococcus pneumoniae*)

Staphylococcus aureus, respiratory, skin and soft-tissue infections. Tetracyclines are not the drug of choice in the treatment of any type of staphylococcal infection.

When penicillin is contraindicated, VIBAZINE DT is an alternative drug in the treatment of infections due to:

Treponema pallidum and *Treponema pertenue* (syphilis and yaws)

Listeria monocytogenes

Clostridium species

Bacillus anthracis

Leptotrichia buccalis (formerly *Fusobacterium fusiforme*), Vincent's infection

Actinomyces species

In acute intestinal amebiasis VIBAZINE DT may be a useful adjunct to amebicides.

In severe acne VIBAZINE DT may be useful adjunctive therapy.

VIBAZINE DT is indicated in the treatment of trachoma, although the infectious agent is not always eliminated, as judged by immunofluorescence.

VIBAZINE DT is indicated for the treatment of Stage I Lyme disease.

Inclusion conjunctivitis may be treated with oral VIBAZINE DT alone, or with a combination of topical agents.

VIBAZINE DT is indicated for the prophylaxis and treatment of leptospirosis.

VIBAZINE DT is indicated for the treatment and selective prophylaxis of cholera.

VIBAZINE DT is indicated for prophylaxis in the following conditions:

scrub typhus (*Rickettsia tsutsugamushi*)

traveller's diarrhea (enterotoxigenic *Escherichia coli*)

malaria (in areas with chloroquine resistant *Plasmodium falciparum*)

2.2 Posology and Method of Administration

Dosage: It must be remembered that the usual dosage and frequency of administration of VIBAZINE DT differs from that of most other tetracyclines. Exceeding the recommended dosage may result in an increased incidence of side effects. Therapy should be continued at least 24 to 48 hours after symptoms and fever have subsided. When used in streptococcal infections, therapy should be continued for 10

days to prevent the development of rheumatic fever or glomerulonephritis.

The usual dose of VIBAZINE DT in adults is 200 mg on the first day of treatment (administered as a single dose or as two doses of 100 mg each) followed by a maintenance dose of 100 mg once daily. In the management of more severe infections (particularly chronic infections of the urinary tract), 200 mg daily should be given throughout the treatment period.

Acne vulgaris: 50-100 mg daily for up to 12 weeks.

Uncomplicated gonococcal infections (except anorectal infections in men): 100 mg by mouth twice daily for 7 days. As an alternative single visit dose, administer 300 mg stat followed in one hour by a second 300 mg dose. The dose should be administered with food, including milk or carbonated beverage, as required.

Uncomplicated urethral, endocervical, or rectal infection in adults caused by *Chlamydia trachomatis*: 100 mg, by mouth, twice daily for 7 days.

Acute epididymo-orchitis caused by *C. trachomatis* or *N. gonorrhoeae* 100 mg by mouth twice a day for at least 10 days. In *Ureaplasma urealyticum* (T-mycoplasma) infections in the male genital tract associated with unexplained infertility, both the infected male and his wife should be treated with 100 mg twice daily for four weeks.

Nongonococcal urethritis caused by *Ureaplasma urealyticum* 100 mg, by mouth, twice daily for 7 days.

Primary and secondary syphilis: 300 mg a day in divided doses for at least 10 days.

Acute pelvic inflammatory disease (PID): 100 mg twice daily for 10-14 days, after initial parenteral therapy with a suitable antibiotic.

For treatment of chloroquine-resistant falciparum malaria: 200 mg daily for at least 7 days. Due to the potential severity of the infection, a rapid-acting schizonticide such as quinine should always be given in conjunction with VIBAZINE DT; quinine dosage recommendations vary in different areas.

For prophylaxis of malaria: 100 mg daily in adults; for children over 8 years of age the dose is 2 mg/kg given once daily up to the adult dose. Prophylaxis can begin 1-2 days before travel to malarious areas. It should be continued daily during travel in the malarious areas and for 4 weeks after the traveller leaves the malarious area.

Tick and louse-borne relapsing fevers and louse-borne typhus have been successfully treated with a single dose of 100 or 200 mg according to severity.

For the prevention of scrub typhus: 200 mg as a single oral dose.

For the treatment and selective prophylaxis of cholera in adults: 300 mg in a single dose.

For the prevention of travelers' diarrhea in adults: 200 mg on the first day of travel (administered as a single dose or as 100 mg every 12 hours) followed by 100 mg daily throughout the stay in the area.

For the treatment of leptospirosis: 100 mg orally twice daily for 7 days.

For the prevention of leptospirosis: 200 mg orally on a weekly basis throughout the stay in the area and 200 mg at the completion of the trip.

Data on the use of the drug prophylactically are not available beyond 21 days.

Dosage in Children: For children above 8 years of age: the recommended dosage schedule for children weighing 50 kg or less is 4 mg/kg of body weight (given as a single daily dose or divided into two doses on the first day of treatment), followed by 2 mg/kg of body weight (given as a single daily dose or divided into two doses), on subsequent days. For more severe infections up to 4 mg/kg of body weight may be used. For children over 50 kg the usual adult dose should be used. (See "Warnings" section about use in children).

Usage in Renal Impairment: Studies to date have indicated that administration of VIBAZINE DT at the usual recommended doses does not lead to excessive accumulation of the antibiotic in patients with renal impairment.

Administration: VIBAZINE DT tablets in the form of doxycycline monohydrate can be taken as such with an adequate amount of fluid or suspended in about 50 ml of water and swallowed.

Administration of adequate amounts of fluid along with tablet forms of drugs in the tetracycline class is recommended to reduce the risk of esophageal irritation and ulceration.

If gastric irritation occurs, it is recommended that VIBAZINE DT be given with food or milk. Studies indicate that the absorption of VIBAZINE DT is not markedly influenced by simultaneous ingestion of food or milk.

2.3 Contraindications

This drug is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines.

2.4 Special Warnings and Special Precautions for Use

Warnings: The use of drugs of the tetracycline class during tooth development (last half of pregnancy, infancy and childhood to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown). This adverse reaction is more common during long term use of the drugs but has been observed following repeated short term courses. Enamel hypoplasia has also been reported. VIBAZINE DT, therefore, should not be used in these groups of patients unless other drugs are not available, are not likely to be effective or are contraindicated.

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. (Patients likely to be exposed to direct sunlight or ultraviolet light should be advised that this reaction can occur with tetracycline drugs, and treatment should be discontinued at the first evidence of skin erythema).

The antianabolic action of the tetracyclines may cause an increase in BUN. Studies to date indicate that this does not occur with the use of

VIBAZINE DT in patients with impaired renal function.

Precautions: The use of antibiotics may occasionally result in overgrowth of nonsusceptible organisms. Constant observation of the patient is essential. If a resistant organism appears, the antibiotic should be discontinued and appropriate therapy instituted.

When treating venereal disease when coexistent syphilis is suspected, proper diagnostic procedures, including dark-field examinations, should be utilized. In all such cases, monthly serological tests should be made for at least four months.

In long-term therapy, periodic laboratory evaluation of organ systems, including hematopoietic, renal, and hepatic studies should be performed.

Infections due to group A beta-hemolytic streptococci should be treated for at least 10 days.

Usage in Children: (See "Warnings" section about use during tooth development). As with other tetracyclines, VIBAZINE DT forms a stable calcium complex in any bone-forming tissue. A decrease in the fibula growth rate has been observed in prematures given oral tetracycline in doses of 25 mg/kg every 6 hours. This reaction was shown to be reversible when the drug was discontinued.

2.5 Interaction with Other Medicaments and Other Forms of Treatment

Because the tetracyclines have been shown to depress plasma prothrombin activity, patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.

Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving VIBAZINE DT in conjunction with penicillin.

Absorption of tetracyclines is impaired by antacids containing aluminum, calcium, or magnesium; iron-containing preparations; and bismuth salts.

Alcohol, barbiturates, carbamazepine, and phenytoin decrease the half-life of VIBAZINE DT.

The concurrent use of tetracyclines and methoxyflurane has been reported to result in fatal renal toxicity.

There have been anecdotal reports that concurrent use of tetracyclines may render oral contraceptives less effective.

2.6 Pregnancy and Lactation

Use in Pregnancy: VIBAZINE DT has not been studied in pregnant patients. It should not be used in pregnant women unless, in the judgement of the physician, it is essential for the welfare of the patient.

Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues and can have toxic effects on the developing fetus (often related to retardation of skeletal development). Evidence of embryotoxicity has also been noted in animals treated early in pregnancy.

Use During Lactation: Tetracyclines are present in the milk of lactating women who are taking a drug of this class and should therefore be avoided in nursing mothers.

2.7 Undesirable Effects

Due to virtually complete absorption of VIBAZINE DT, gastrointestinal side effects are infrequent. The following adverse reactions have been observed in patients receiving tetracyclines.

Gastrointestinal: anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia, enterocolitis, and inflammatory lesions (with monilial overgrowth) in the anogenital region. Abnormal hepatic function has been reported rarely. These reactions have been caused by both the oral and parenteral administration of tetracyclines. Rare instances of esophagitis and esophageal ulcerations have been reported in patients receiving tablet forms of drugs in the tetracycline class. Most of these patients took medications immediately before going to bed.

Skin: maculopapular and erythematous rashes. Exfoliative dermatitis has been reported but is uncommon. Photosensitivity is discussed in the "Warnings" section.

Renal Toxicity: Rise in BUN has been reported with tetracyclines and is apparently dose related. (See "Warnings").

Hypersensitivity reactions: urticaria, angioneurotic edema, anaphylaxis, anaphylactoid purpura, serum sickness, pericarditis, and exacerbation of systemic lupus erythematosus.

Bulging fontanels in infants and benign intracranial hypertension in adults have been reported in individuals receiving full therapeutic dosages. These conditions disappeared rapidly when the drug was discontinued.

Blood: hemolytic anemia, thrombocytopenia, neutropenia, and eosinophilia have been reported with tetracyclines.

When given over prolonged periods, tetracyclines have been reported to produce brown-black microscopic discoloration of thyroid glands. No abnormalities of thyroid function studies are known to occur.

2.8 Overdosage

In case of overdosage, discontinue medication, treat symptomatically and institute supportive measures. Dialysis does not alter serum half-life and thus would not be of benefit in treating cases of overdosage.

3. PHARMACOLOGICAL PROPERTIES

VIBAZINE DT has a high degree of lipoid solubility and a low affinity for calcium binding. It is highly stable in normal human serum.

VIBAZINE DT will not degrade into an epianhydro form.

3.1 Pharmacodynamic Properties

VIBAZINE DT is primarily bacteriostatic and is thought to exert its antimicrobial effect by the inhibition of protein synthesis. VIBAZINE DT is active against a wide range of gram-positive and gram-negative microorganisms.

3.2 Pharmacokinetic Properties

Absorption: Tetracyclines are readily absorbed and are bound to plasma proteins in varying degrees. VIBAZINE DT is virtually completely absorbed after oral administration. Studies reported to date indicate that the absorption of VIBAZINE DT, unlike certain other tetracyclines, is not notably influenced by the ingestion of food or milk.

Biotransformation/Elimination: VIBAZINE DT is concentrated by the liver in the bile, and excreted in the urine and feces in high concentrations.

Following a 200 mg dose, normal adult volunteers averaged peak serum levels of 2.6 μg/ml of VIBAZINE DT at 2 hours decreasing to 1.45 μg/ml at 24 hours. Excretion of VIBAZINE DT by the kidney is about 40%/72 hours in individuals with normal renal function (creatinine clearance about 75 ml/min). This percentage excretion may fall to a range as low as 1-5%/72 hours in individuals with severe renal insufficiency (creatinine clearance below 10 ml/min). Studies have shown no significant difference in serum half-life of VIBAZINE DT (range 18 to 22 hours) in individuals with

normal and severely impaired renal function. Hemodialysis does not alter the serum half-life of VIBAZINE DT.

4. PHARMACEUTICAL PARTICULARS

4.1 List of Excipients

Inert ingredients in VIBAZINE DT Tablets include microcrystalline cellulose, carboxymethylcellulose sodium, silicon dioxide, and magnesium stearate.

4.2 Shelf Life

VIBAZINE DT Tablets should be used within 2 years from the date of manufacture.

4.3 Special Precautions for Storage/Storage Conditions

Store in a cool, dry place.

4.4 Nature and Contents of Container

VIBAZINE DT Tablets 100 mg: strips of 2 tablets each, in cartons of 30 strips each.

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Pfizer Inc., U.S.A.